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(54) CLATHRATE PROSTAGLANDINS AND COMPOSITIONS CONTAINING SAME

(71) We, ONO PHARMACEUTICAL CO. LTD., a Japanese Body Corporate, of 14 Doshomachi 2-Chome, Higashiku, Osaka 541, Japan, do hereby declare the invention for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

This invention relates to cyclodextrin clathrates of prostaglandins or derivatives thereof, to a process for producing such clathrates and to pharmaceutical compositions containing them. It is an improvement in or modification of the invention described and claimed in the specification of our Application No. 19785/71 (now Serial No. 1,351,238).

In the specification of Application No. 19785/71 (now Serial No. 1,351,238) we have claimed cyclodextrin clathrates of prostaglandins or of derivatives of prostaglandins, and specifically the β-cyclodextrin clathrates of PGE_1 alcohol, PGE_1 decyl ester, α-methyl-PGE_1, PGE_2, PGE_2 decyl ester, PGE_2 9-ethoxycarbonylnonyl ester, α-methyl-PGE_2, 15-methyl-PGE_2, 16-methyl-PGE_2(B) 17-methyl-PGE_2(B), 16-methyl-PGE_2(B) alcohol, 16-methyl-PGE_2(B) decyl ester, $PGF_{2\alpha}$, PGA_2 and PGA_2 decyl ester, the β-cyclodextrin clathrate of 9 - oxo - 15α-hydroxyprosta - 5 - *cis*,11,13 - *trans* - trienoic acid, and the α-cyclodextrin clathrates of PGE_2 and PGE_1 alcohol. The cyclodextrin clathrates of prostaglandins and derivatives thereof are solid, white powdery substances much more stable than the prostaglandins themselves, and this stability is of substantial importance in the formulation of pharmaceutical compositions for therapeutic applications, the pharmacological properties of the prostaglandins or derivatives thereof not being impaired by the formation of clathrates.

As a result of further research and experimentation, we have prepared cyclodextrin clathrates of other prostaglandins, and the present invention is concerned with the hitherto unprepared cyclodextrin clathrates of PGE_1, 15-methyl-PGE_1, 16-methyl-PGE_1(B), 17-methyl-PGE_1(B), $PGF_{1\alpha}$ and PGA_1, and more particularly the β-cyclodextrin clathrates of said prostaglandins, which all possess outstanding pharmacological properties, and are highly stable. It is to be understood hereinafter that the expression "cyclodextrin clathrates of prostaglandins of the present invention" means the cyclodextrin clathrates of PGE_1, 15-methyl-PGE_1, 16-methyl-PGE_1(B), 17-methyl-PGE_1(B), $PGF_{1\alpha}$ and $PGA_{1\alpha}$ only.

The explanation of the suffix "(B)" after "16-methyl-PGE_1" is as follows:—

When 16-methyl-PGE_1 is prepared a mixture of four stereoisomers is obtained due to the configuration of the hydroxy and methyl groups on the C-15 and C-16 carbon atoms respectively. The product when subjected to chromatography on a silica gel column can be divided into two portions, one portion having the higher polarity is termed "16-methyl-PGE_1(B)"; its stereo-configuration being unknown.

A similar explanation for the suffix "(B)" after "17-methyl-PGE_1" applies.

The percentage of prostaglandin in the cyclodextrin clathrates of prostaglandins of the present invention can vary considerably, but is suitably from 2% to 12% by weight. The cyclodextrin forming the clathrates can be α-, β- or γ-cyclodextrin, or a mixture of any two or three of them, but preferably β-cyclodextrin is used.

The cyclodextrin clathrates of prostaglandins of the present invention can be prepared by reacting cyclodextrin with PGE_1, 15-methyl-PGE_1, 16-methyl-PGE_1(B), 17-methyl-PGE_1(B), $PGF_{1\alpha}$ or PGA_1.

In preparing the clathrate compounds, cyclodextrin is preferably dissolved in water and/or in an organic solvent which is miscible with water and the solution added to a said prostaglandin dissolved in an organic solvent which is miscible with water, e.g. ethanol.

[*Price 33p*]

After the mi[illegible]s heated, the clathrate product may be obtained by concentrating the mixture under reduced pressure or leaving it to cool. Preferably 4 to 12 moles of cyclodextrin are used for each mole of prostaglandin. The mixing ratio of organic solvent with water may be suitably varied according to the solubilities of the starting materials and clathrate products. Due to the low thermostabilities of the prostaglandin molecules, it is preferable to conduct the reaction at a temperature below 70° C. In the case of the PGE compounds, the preferred reaction temperature is 20—60° C.

The invention will be illustrated by the following Examples.

EXAMPLE 1.

A solution prepared by heating and dissolving 248 mg. of β-cyclodextrin in 2.8 ml. of water was added to a solution prepared by dissolving 18.0 mg. of PGE_1 in 0.4 ml. of ethanol. After the mixture was heated to dissolution at 60° C., it was cooled to room temperature to obtain a precipitate. After standing overnight at room temperature, the precipitate was recovered by filtration and washed with 50% aqueous ethanol and dried under reduced pressure to obtain 203 mg. of the desired clathrate product. The content of PGE_1 in the product was 7.8%.

EXAMPLE 2.

A solution prepared by heating and dissolving 253 mg. of β-cyclodextrin in 2.8 ml. of water was added to a solution prepared by dissolving 18.1 mg. of $PGF_{1\alpha}$ in 0.4 ml. of ethanol. The mixture was heated to dissolution at 60° C., and then treated in the same manner as described in Example 1 to obtain 211 mg. of the desired clathrate product. The content of $PGF_{1\alpha}$ in the product was 2.4%.

EXAMPLE 3.

A solution prepared by heating and dissolving 240 mg. of β-cyclodextrin in 2.8 ml. of water was added to a solution prepared by dissolving 16.8 mg. of PGA_1 in 0.8 ml. of ethanol. The mixture was heated to dissolution at 60° C., and then treated in the same manner as described in Example 1 to obtain 183 mg. of the desired clathrate product. The content of PGA_1 in the product was 7.6%.

EXAMPLE 4.

A solution prepared by heating and dissolving 240 mg. of β-cyclodextrin in 2.8 ml. of water was added to a solution prepared by dissolving 18.4 mg. of 15-methyl-PGE_1 in 0.4 ml. of ethanol. The mixture was heated to dissolution at 60[illegible] and then treated in the same manner as described in Example 1 to obtain 195 mg. of the desired clathrate product. The content of 15-methyl-PGE_1 in the product was 2.1%.

EXAMPLE 5.

A solution prepared by heating and dissolving 245 mg. of β-cyclodextrin in 2.8 ml. of water was added to a solution prepared by dissolving 18.5 mg. of 16-methyl-PGE_1(B) in 0.4 ml. of ethanol. The mixture was heated to dissolution at 60° C. and then treated in the same manner as described in Example 1 to obtain 170 mg. of the desired clathrate product. The content of 16-methyl-PGE_1(B) in the product was 10.2%.

EXAMPLE 6.

A solution prepared by heating and dissolving 250 mg. of β-cyclodextrin in 2.8 ml. of water was added to a solution prepared by dissolving 18.9 mg. of 17-methyl-PGE_1(B) in 0.4 ml. of ethanol. The mixture was heated to dissolution at 60° C., and then treated in the same manner described in Example 1 to obtain 168 mg. of the desired clathrate product. The content of 17-methyl-PGE_1(B) in the product was 9.8%.

In all of the above Examples, the clathrate compounds obtained were white powdery substances and their infrared spectra showed absorptions of carbonyl groups at 1710—1740 cm^{-1} in the case of the PGEs and PGA_1. The binding ratios of the prostaglandins with cyclodextrin in the clathrates (i.e. content of prostaglandin in the products) were determined by quantitative analysis of the prostaglandins in the clathrate compounds. The quantitative analysis was conducted in the following manner:— PGA_1 and the PGE_1 compounds were isomerized with alkali to PGB compounds and the resulting absorption values in UV spectra were determined at wavelength 278 mμ. In the case of $PGF_{1\alpha}$, a contraction of guinea pig colon was employed in the determination.

It was confirmed by heat stability tests that the cyclodextrin clathrates of prostaglandins of the present invention have better, or substantially better, stability than the original prostaglandins, and this improvement in stability is particularly noticeable in respect of the PGE_1 compounds.

The following Table shows the contents of the various PGs in clathrate compounds of the present invention and the results of stability tests when the clathrates and original prostaglandins were heated at 106 ± 4° C.

TABLE

Prostaglandin	Content*	Heat Stability**		
		1 hour	3 hours	8 hours
PGE_1-β-CD	7.8	98.0	91.2	90.3
PGE_1		80.2	57.2	28.2
15-methyl-PGE_1-β-CD	2.1	88.2	87.8	84.0
15-methyl-PGE_1		68.0	48.3	40.6
16-methyl-PGE_1(B)-β-CD	10.2	96.5	92.0	86.2
16-methyl-PGE_1(B)		73.2	63.5	48.0
17-methyl-PGE_1(B)-β-CD	9.8	97.8	97.5	97.0
17-methyl-PGE_1(B)		75.3	68.2	61.2
$PGF_{1\alpha}$-β-CD	2.3	100	100	99
$PGF_{1\alpha}$		100	99	99
PGA_1-β-CD	7.6	99.8	98.8	98.0
PGA_1		99.5	98.3	95.0

"CD" is an abbreviation for "cyclodextrin clathrate".

* The figures indicate the percentage (w/w) of prostaglandin in the clathrates.

** The figures indicate the percentage of prostaglandin remaining stable at 106°±4°C.

As the cyclodextrin clathrates of prostaglandins of the present invention, which possess the pharmacological properties of the original prostaglandins, are white powdery substances and are easy to handle they may be employed in various pharmaceutical formulations, e.g. injectable compositions, tablets, aerosols, powders, capsules or suspensions. The present invention accordingly provides as another feature of it, pharmaceutical compositions containing, as the active ingredient, a cyclodextrin clathrate of prostaglandins of the present invention in association with a pharmaceutical carrier.

WHAT WE CLAIM IS:—

1. Cyclodextrin clathrates of PGE_1, 15-methyl-PGE_1, 16-methyl-PGE_1(B), 17-methyl-PGE_1(B), $PGF_{1\alpha}$ and PGA_1.

2. β-Cyclodextrin clathrates of PGE_1, 15-methyl-PGE_1, 16-methyl-PGE_1(B), 17-methyl-PGE_1(B), $PGF_{1\alpha}$ and PGA_1.

3. Cyclodextrin clathrates of a prostaglandin according to claim 1 or 2 in which the prostaglandin content of the clathrate is from 2% to 12% by weight of the clathrate.

4. A process for the production of a cyclodextrin clathrate of a prostaglandin as claimed in claim 1 which comprises reacting PGE_1, 15-methyl-PGE_1, 16-methyl-PGE_1(B), 17-methyl-PGE_1(B), $PGF_{1\alpha}$ or PGA_1, with cyclodextrin.

5. A process according to claim 4 in which a solution of the cyclodextrin in water and/or in an organic solvent which is miscible with water is added to a solution of the prostaglandin in an organic solvent which is miscible with water, the mixture is heated at a temperature below 70° C., and the resulting cyclodextrin clathrate of the prostaglandin is separated from the reaction mixture.

6. A process according to claim 5 in which the prostaglandin is PGE_1, 15-methyl-PGE_1, 16-methyl-PGE_1(B) or 17-methyl-PGE_1(B) and the reaction is carried out at a temperature of 20—60° C.

7. A process according to claim 5 or 6 in which the organic solvent is ethanol.

8. A process according to any one of claims 4 to 7 in which the molar ratio of prostaglandin to cyclodextrin in the reaction mixture is 1:4 to 12.

9. A process according to any one of claims 4 to 8 in which the cyclodextrin is β-cyclodextrin.

10. A process for the production of cyclodextrin clathrates of prostaglandins according to claim 4 substantially as hereinbefore described in any one of Examples 1 to 6.

11. Cyclo[redacted]in clathrates of prostaglandins as claimed [redacted]im 1 when produced by the process claimed in any one of claims 4 to 10.

12. Pharmaceutical compositions which comprise, as active ingredient, a cyclodextrin clathrate of a prostaglandin as claimed in claim 1, 2 or 3 in association with a pharmaceutically acceptable carrier.

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